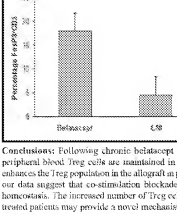

Conclusions: Following chronic belatacept therapy, the number and function of peripheral blood Treg cells are maintained in kidney transplant patients. Belatacept enhances the Treg population in the allograft in patients with acute rejection. Therefore, our data suggest that co-stimulation blockade with belatacept does not affect Treg homeostasis. The increased number of Treg cells in rejecting allografts in belatacept-treated patients may provide a novel mechanism whereby belatacept can mitigate the severity of acute rejection and improve graft survival.

Abstract# 282

mTOR Inhibition Reduces the Number of Colony-Forming Units of Erythroid Progenitor Cells.

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Introduction:

mTOR inhibition has been associated with microcytosis and/or anemia in kidney transplant patients. The aim was to evaluate the influence of mTOR inhibition on erythropoiesis in kidney transplant patients and healthy controls.

Methods

Erythroid progenitor cells were isolated from peripheral blood of healthy control persons (HC; n=8), or kidney transplant patients with chronic sirolimus treatment with (SRL+MC; n=8) or without microcytosis (SRL-MC; n=8). The isolated progenitor cells were then cultured in a semi-solid medium, containing 3 U/ml erythropoietin, in the absence or presence of SRL (5ng/mL) for 14 days. Burst forming unit erythroid (BFU-E) derived colonies were then counted through an inverted microscope considering that each colony consists of more than 40 cells. Cultures were performed in duplicate and colonies were counted in the entire culture dish

Results.

Hemoglobin was 13.1 (SRL+MC) and 13.5 (SRL-MC) g/dL (p=ns). RBC count was 5.1 and 4.7x10^6/µL in SRL+MC and SRL-MC respectively (p=0.034). MCV was 76 in SRL+MC and 87 fL in SRL-MC (p< 0.0001). Presence of SRL in the culture medium led to a decreased number of colonies in healthy controls and kidney transplant patients (without SRL: 34.2±11.4 vs. with SRL: 27.5±9.9 BFU-E derived colonies p=0.03). The same difference was seen if the three groups were analyzed separately (HC, SRL-MC, SRL +MC). Interestingly, culture dishes of SRL +MC patients tended to contain an increased number of colonies when cultured in the absence of SRL when compared to SRL-MC and HC (39.9 vs 29.9 p>0.17), which might indicate that microcytic patients present an increased number of circulating progenitor cells.

Conclusion: mTOR inhibition leads to a reduced number of erythroid colonies in culture; microcytosis in SRL treated patients (if it occurs) might be compensated by a higher number of erythrocytes and circulating progenitor cells.

Abstract# 283

Steady-State Pharmacokinetics of the Protein Kinase C Inhibitor AEB071 in De Novo Kidney Transplant Patients.

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The steady-state pharmacokinetics of the protein kinase C inhibitor AEB071 were characterized in the context of a randomized, multicenter trial in de novo kidney transplant recipients. A total of 63 evaluable patients received 200 mg bid AEB071 in a multidrug immunosuppressive regimen. An AUC-profile was obtained on day 8 posttransplant and blood samples were measured at a central laboratory for concentrations of AEB071 and its pharmacologically active N-desmethyl metabolite. Data were compared to those previously characterized in psoriasis patients receiving 200 mg bid AEB071 as monotherapy. **Drug exposure:** As tabulated below, steady-state drug exposure in renal transplant patients was similar to that in psoriasis patients (p=NS for all parameters). This exposure was associated with a significant clinical response (35% reduction in PASI score vs placebo) in the psoriasis trial (see ATC 2007 abstract 1723).

Parameter	Renal transplant patients (n=63)	Psoriasis patients (n=6)
C0 (ng/ml)	381 ± 298	400 ± 66
tmax (h)	2 (1 - 6)	2 (1 - 4)
Cmax (ng/ml)	1560 ± 649	1163 ± 536
AUC (tau,h/ml)	9780 ± 4820	7837 ± 3877

The steady-state AUC of N-desmethyl-AEB071 was minor in comparison to AEB071 and similar between the patient groups (200 ± 90 ng h/ml in transplantation vs 393 ± 220 ng.h/ml in psoriasis (p=0.08). **Demographic covariates:** In the first week posttransplant with patients receiving fixed-dose AEB071, intersubject variability for C0 was 78% and for AUC was 49%. AUCs were similar in men vs women (8350 ± 4163 vs 10784 ± 5369, p=0.26). Age, which ranged from 18-64 years, did not influence AUC based on regression analysis (r^2 = 0.005, p=0.65). There was a borderline-significant negative correlation between weight (range, 51-110 kg) and AUC (p = 0.07); however, its clinical relevance was low in that it could explain <9% of the variability in AUC (r^2 = 0.086). There was a significant positive correlation between AEB071 C0 and AUC (r^2 = 0.724, p<0.001)

Conclusions: (1) In the first week posttransplant, patients achieved AEB071 blood levels anticipated for this regimen. (2) There was notable intersubject pharmacokinetic variability at this time but it was not attributable to standard demographic factors such as sex, age, or weight. (3) A good correlation was noted between C0 and AUC suggesting that C0 might serve as a marker for total drug exposure.

Abstract# 284

A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP-Tacro 2 mg Tablets (q.d.) Versus Advagraf® 2 x 1 mg Capsules (q.d.) in Normal, Healthy, Caucasian Male Subjects.

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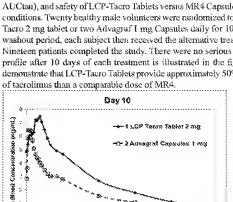
Extended release of tacrolimus along different intestinal regions could lower the inter-subject variability of drug absorption, increase bioavailability, and potentially improve the therapeutic use of the product. LCP-Tacro™ Tablets (LifeCycle Pharma) are a modified/extended release (MR) formulation of tacrolimus produced using MeltDose®, a novel proprietary technology that increases the bioavailability of low water soluble drugs via the solid formulation of drug substance at the molecular state.

In phase 1 studies in healthy volunteers, LCP-Tacro Tablets™ demonstrated approximately a 50% greater bioavailability than Prograf® Capsules (Astellas Pharma, Japan) and a PK profile supporting once-a-day administration. Advagraf® (MR+, Astellas Pharma) is also a modified, extended release formulation of tacrolimus designed for once-a-day administration. This study is a phase 1, two-way crossover, open label, multidose, bioequivalence study to compare the pharmacokinetics (Cmax, C24, and AUCtau), and safety of LCP-Tacro Tablets versus MR+ Capsules in steady state, fasting conditions. Twenty healthy male volunteers were randomized to receive either one LCP-Tacro 2 mg tablet or two Advagraf 1 mg Capsules daily for 10 days. After a two week washout period, each subject then received the alternative treatment.

Nineteen patients completed the study. There were no serious adverse events. The PK profile after 10 days of each treatment is illustrated in the figure below. The results demonstrate that LCP-Tacro Tablets provide approximately 50% greater bioavailability of tacrolimus than a comparable dose of MR+.



Kidney Immunosuppression: Minimization – Avoidance Protocols

Abstract# 285

Extended Enrollment and Analysis of a Prospective Steroid-Free Immunosuppression Trial Supports Study Safety and Efficacy.

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AIM: To evaluate the long-term safety and efficacy of a prospective, single-center, pilot, steroid-free (SF) pediatric renal transplantation.

METHODS: 112 consecutive pediatric renal transplant recipients of living (n=88) and deceased donors were enrolled since 1999 in a steroid avoidance protocol with extended Daclizumab induction (6mo), FAC and MMF. 105 matched recipients on a steroid-based